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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,416	LIU, XIANGJUN	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *October 20, 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *21042003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed October 20, 2003. Claims 22-32 were previously pending. Applicant amended claims 22, 25-32 and added new claims 33-39. Claims 22-39 are pending and will be examined.

2. The IDS filed April 21, 2003 has been considered.

3. The drawings were received on October 20, 2003 (corrected Fig. 1, 2A, 2B and 3). These drawings are accepted.

4. Applicant's amendments to specification presented on pages 4 and 5 of the response (paragraphs [0052], [0072], [0068], [0069] and [0073]) overcame the objections raised in the previous office action.

5. Applicant's amendments overcame the rejection of claims 22-32 under 35 U.S.C. 112, second paragraph. All other rejections are maintained for reasons given in the "Response to Arguments" section.

Response to Arguments

6. Applicant's arguments filed October 20, 2003 have been fully considered but they are not persuasive.

A) Regarding rejection of claims 22-29, 31 and 32 under 35 U.S.C. 102 (e) over Van Ness et al., Applicant argues the following:

a) Van Ness et al. do not anticipate present claims because they do not teach spacer located internally to an oligonucleotide sequence.

b) Van Ness et al. do not teach fluorescent beads, or beads that have a fluorescence color ratio.

Regarding a), this feature is not claimed. In addition, even if this feature was claimed, Van Ness et al. teach spacers located internally to oligonucleotide sequence (for example, col. 39, lines

45-67; col. 40, lines 1-41; col. 42, lines 53-56). Further, the term "spacer" is very broad, encompassing, for example, a single nucleotide separating two different regions of an oligonucleotide, which is also taught by Van Ness et al. (see col. 40, lines 30-41; col. 44, lines 61, 62).

Regarding b), claim 32 does not require that the beads themselves are fluorescent. Therefore, Van Ness et al. anticipate the claim by teaching beads to which fluorescently-labeled oligonucleotides are attached (see col. 75, lines 49-62 and col. 83, lines 10-67). Further, Van Ness et al. specifically teach determination of the fluorescence color ratios (see col. 83, lines 55-61, Table 13). Therefore, Van Ness anticipates claims 32 and the newly added claim 38.

The rejections are maintained.

7. B) Regarding rejection of claims 22-29, 31 and 32 under 35 U.S.C. 103(a) over Van Ness et al. and Kaneoka et al. and rejection of claim 30 under 35 U.S.C. 103(a) over Van Ness et al., Kaneoka et al. and Nolan et al., Applicant argues that this combination of references fails to render the claims obvious, since Van Ness et al. do not teach present spacer configuration. This argument was addressed above. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of the references which renders the claims obvious. Thus, since Kaneoka et al. teach detection of HLA alleles by hybridization, and Van Ness et al. teach that hybridization efficiency improves by addition of spacers to the oligonucleotides serving as hybridization probes, one of ordinary skill in the art would be motivated to use the oligonucleotides with spacers in the method of Kaneoka et al.

The rejections are maintained.

C) Regarding rejection of claims 22-29 and 32 under 35 U.S.C. 103(a) over Van Ness et al. and Armstrong et al., and rejection of claim 31 under 35 U.S.C. 103(a) over Van Ness et al., Armstrong et al. and Long, Applicant argues that this combination of references fails to render the claims obvious, since Van Ness et al. do not teach present spacer configuration. These arguments were addressed above.

The rejections are maintained.

Specification

8. The amendment filed October 20, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: newly added paragraphs [0074.1]-[0074.18].

Applicant states in the Reply that these paragraphs were added to include all essential material incorporated by reference. However, the material referred to in the previous office action was "Current Protocols in Molecular Biology" by Ausubel et al., which Applicant cites in paragraph [0037] as being incorporated by reference. Therefore, including material incorporated by reference means including passages from the reference, i.e., from the "Current Protocols in Molecular Biology" by Ausubel et al., not adding new examples in the experimental section.

Applicant is required to cancel the new matter in the reply to this Office Action.

Incorporation by Reference

9. Applicant indicated on page 7, [0030], that all patents and references cited are incorporated by reference. On page 9, [0037], Applicant cites "current Protocols in Molecular Biology" by Ausubel et al. and makes a statement that the teachings of the reference are incorporated by reference. On page 24, [0077], Applicant states that the references cited are incorporated into the patent application in their entirety.

10. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference (emphasis added). The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

11. If the publications cited constitute a non-essential material, Applicant should include a statement to this effect (see MPEP 608.01(p), part A of which is cited below).

MPEP 608.01(p).

A. Review of Applications Which Are To Issue as Patents.

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, Ex parte Schwarze, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.

Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, hyperlinks and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § 608.01. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Claim interpretation

12. As indicated by Applicants, the interpretation of the limitation in claim 22: "wherein the oligonucleotides that are coupled to different bead sets are oligonucleotides with and without a spacer", is that "all combinations of oligonucleotides with and without spacers coupled to bead sets are permissible in the claimed invention so long as the claimed method can be effectively performed" (Reply, page 16, third paragraph).

13. The term "random bases" is not defined, therefore it is interpreted as any bases.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 22-29 and 31-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Van Ness et al. (U. S. Patent No. 6,361,940 B1; cited in the previous office action).

Regarding claim 22, Van Ness et al. teach combinations of oligonucleotides with different spacers which may be used in any reaction involving hybridization, such as genetic screening and amplification reactions (col. 44, lines 59-67; col. 45, lines 1-3). In particular, such reactions include allele-specific PCR (amplification with allele-specific primers; col. 46, lines 27-33), DNA sequencing (col. 47, lines 38-42), PCR (col. 49, lines 63-67), single-nucleotide primer extension (col. 51, lines 62-67; col. 52, lines 1-5; col. 55, lines 65-67; col. 56, lines 1-14; col. 61, lines 1-40). A single nucleotide polymorphism (SNP) detection assay can be performed by hybridizing two different primers (differing in sequence and labels) to a target oligonucleotide, extending the

primers using a polymerase, separating primers which were extended from primers which were not and determining the amounts of first and second labels in the primers that have been extended (col. 60, lines 34-67).

Van Ness et al. teach an array of oligonucleotides immobilized on solid support, each of the nucleotides comprising a specificity spacer (col. 11, lines 53-67; col. 12, lines 1-37; Fig. 26). The specificity spacer may contain a base analog, so that a polymerase will continue through the spacer, or may contain an abasic residue, which terminates polymerase transcription (col. 40, lines 28-41). The specificity spacer may contain a component with 2-5 carbons (col. 40, lines 42-67; col. 41, lines 1-39). Oligonucleotides may have a plurality of specificity spacers (col. 41, lines 40-55). A specificity spacer site may be located approximately in a middle of a primer (col. 42, lines 53-67). Specificity spacers increase specificity of primer or probe annealing to targets (col. 42, lines 12-34). The solid support can take form of beads or membranes (col. 71, lines 65-67; col. 72, lines 1-14).

Regarding claim 23, Van Ness et al. teach separation of allele-specific nucleic acid fragments (col. 60, lines 64, 65; col. 61, lines 26-30).

Regarding claims 24-26, 32, 37 and 38, Van Ness et al. teach oligonucleotides specific for two different base-pair mismatches, i.e., containing different spacers, coupled to different bead sets labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red. Oligonucleotides specific for the wild-type sequence did not have a spacer. After hybridization of the probes to target oligonucleotide the probes are denatured and fluorescence is measured in a fluorometer, and results are expressed as fluorescence ratios (col. 75, lines 49-62; col. 83, lines 10-67).

Regarding claim 27, Van Ness et al. teach polymorphism detection is samples containing CYP2D6 gene with 8 polymorphic sites (col. 97, lines 36-52).

Regarding claim 28, Van Ness et al. teach amplifying the gene fragment containing all of the polymorphisms (col. 98, lines 55-67).

Regarding claim 29, Van Ness et al. teach denaturing the target nucleic acid (col. 98, lines 9-11).

Regarding claim 31, Van Ness et al. teach HLA alleles (col. 63, lines 25-44).

Regarding claim 33 and 34, Van Ness et al. teach the spacer being nucleic acid bases (col. 40, lines 30-41; col. 44, lines 61, 62).

Regarding claim 35, Van Ness et al. teach the spacer in the middle of oligonucleotide sequence (col.. 42, lines 53-56).

Regarding claim 36, Van Ness et al. teach oligonucleotides with perfect sequence homology to their target oligonucleotides (col. 18, lines 39-41, lines 61-63; col. 19, lines 16-18).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 22-29 and 31-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneoka et al. (Biotechniques, vol. 10, p. 30, 32, 34, 1991; cited in the previous office action) and Van Ness et al. (U. S. Patent No. 6,361,940 B1; cited in the previous office action).

A) Regarding claims 22 and 31, Kaneoka et al. teach detection of HLA alleles by hybridizing a target nucleic acid with oligos, i.e., allele-specific primers (PSP 25 and Amp 1) coupled to bead sets to form a complex, followed by assaying the complex products (page 30, continued on page 32; page 32, second and third paragraphs).

Regarding claim 23, Kaneoka et al. teach separation of the allele-specific nucleic acid fragments on a sequencing gel (page 32, Figure 1).

Regarding claim 27, Kaneoka et al. teach purification of DNA containing the HLA-DR alleles (HLA-DRB1*0401-0408) from peripheral white blood cells (page 32, first paragraph).

Regarding claim 28, Kaneoka et al. teach amplification of the DNA with primers PSP 25 or Amp 1 (page 32, second paragraph).

Regarding claim 29, Kaneoka et al. teach converting double-stranded DNA to single-stranded DNA by denaturation (page 32, second paragraph).

B) Kaneoka et al. do not teach oligonucleotides with and without spacers coupled to different bead sets.

C) Van Ness et al. teach compositions and methods for increasing specificity of hybridization reactions.

Regarding claim 22, Van Ness et al. teach an array of oligonucleotides immobilized on solid support, each of the nucleotides comprising a specificity spacer (col. 11, lines 53-67; col. 12, lines 1-37; Fig. 26). The specificity spacer may contain a base analog, so that a polymerase will continue through the spacer, or may contain an abasic residue, which terminates polymerase transcription (col. 40, lines 28-41). The specificity spacer may contain a component with 2-5 carbons (col. 40, lines 42-67; col. 41, lines 1-39). Oligonucleotides may have a plurality of specificity spacers (col. 41, lines 40-55). A specificity spacer site may be located approximately in a middle of a primer (col. 42, lines 53-67). Specificity spacers increase specificity of primer or probe annealing to targets (col. 42, lines 12-34). The solid support can take form of beads or membranes (col. 71, lines 65-67; col. 72, lines 1-14).

Van Ness et al. teach that combinations of oligonucleotides with different spacers may be used in any reaction involving hybridization, such as genetic screening, amplification reactions (col. 44, lines 59-67; col. 45, lines 1-3). In particular, such reactions include allele-specific PCR (amplification with allele-specific primers; col. 46, lines 27-33), DNA sequencing (col. 47, lines 38-

42), PCR (col. 49, lines 63-67), single-nucleotide primer extension (col. 51, lines 62-67; col. 52, lines 1-5; col. 55, lines 65-67; col. 56, lines 1-14; col. 61, lines 1-40). A single base polymorphism detection assay can be performed by hybridizing two different primers (differing in sequence and labels) to a target oligonucleotide, extending the primers using a polymerase, separating primers which were extended from primers which were not and determining the amounts of first and second labels in the primers that have been extended (col. 60, lines 34-67).

Regarding claims 24-26, 32, 37 and 38, Van Ness et al. teach oligonucleotides specific for two different base-pair mismatches, i.e., containing different spacers, coupled to different bead sets labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red. Oligonucleotides specific for the wild-type sequence did not have a spacer. After hybridization of the probes to target oligonucleotide the probes are denatured and fluorescence is measured in a fluorometer, and results are expressed as fluorescence ratios (col. 75, lines 49-62; col. 83, lines 10-67).

Regarding claim 27, Van Ness et al. teach polymorphism detection is samples containing CYP2D6 gene with 8 polymorphic sites (col. 97, lines 36-52).

Regarding claim 28, Van Ness et al. teach amplifying the gene fragment containing all of the polymorphisms (col. 98, lines 55-67).

Regarding claim 29, Van Ness et al. teach denaturing the target nucleic acid (col. 98, lines 9-11).

Regarding claim 31, Van Ness et al. teach HLA alleles (col. 63, lines 25-44).

Regarding claim 33 and 34, Van Ness et al. teach the spacer being nucleic acid bases (col. 40, lines 30-41; col. 44, lines 61, 62).

Regarding claim 35, Van Ness et al. teach the spacer in the middle of oligonucleotide sequence (col.. 42, lines 53-56).

Regarding claim 36, Van Ness et al. teach oligonucleotides with perfect sequence homology to their target oligonucleotides (col. 18, lines 39-41, lines 61-63; col. 19, lines 16-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used beads coupled to oligonucleotides with and without spacers of Van Ness et al. in the method of HLA-DR typing of Kaneoka et al. The motivation to do so, provided by Van Ness et al., would have been that using oligonucleotides with spacers provided increased specificity of primer or probe annealing to target (col. 42, lines 12-34), therefore allowing for accurate determination of allelic sequences.

18. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kaneoka et al. and Van Ness et al. as applied to claim 22 above, and further in view of Nolan et al. (Nature Biotech., vol. 16, pp. 633-638, 1998; cited in the previous office action).

A) Claim 30 is drawn to confirming a sequence of the template by hybridizing the template with a second bead set complementary to the template and measuring hybridization of the templates by flow cytometry.

B) Regarding claim 30, Kaneoka et al. teach sequencing of the amplified target nucleic acids using the Amp 1 primer (page 32, third paragraph). Neither Kaneoka et al. nor Van Ness et al. teach detection of hybridization complexes by flow cytometry.

C) Nolan et al. teach flow cytometry for detection of molecular interactions, including assay for oligonucleotide hybridization on microspheres, which has been used to detect single nucleotide polymorphisms (page 637, fifth paragraph; Fig. 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used flow cytometry of Nolan et al. to detect hybridization complexes of the combined method of Kaneoka et al. nor Van Ness et al. The motivation to do so, provided by Nolan et al., would have been that flow cytometry discriminated between free and bound ligands

without a washing step, had excellent sensitivity, and was used for multiplexing of detection reactions (page 634, second and third paragraphs; page 637, fourth paragraph).

19. Claims 22-29 and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armstrong et al. (Cytometry, vol. 40, pp. 102-108, June 1, 2000; cited in the previous office action) and Van Ness et al. (U. S. Patent No. 6,361,940 B1; cited in the previous office action).

A) Regarding claim 22, Armstrong et al. teach detecting SNPs (=alleles) using oligonucleotide probes coupled to fluorescently encoded microspheres (= beads). The probes are hybridized to fluorescently labeled PCR reaction products and the results are analyzed in a flow cytometer (Abstract). For each SNP, 15-17 probes were used, with each of the four dNTPs substituted for the variant base located in the middle of the probe, and each probe sequence was coupled to a fluorescently tagged microsphere. PCR-amplified genomic DNA was labeled with fluorescein, hybridized to the probes and, after washing away of the unbound PCR products, detected by flow cytometry (Fig. 1; page 102, the last paragraph, continued on page 103; page 103, the first paragraph).

Regarding claim 23, Armstrong et al. teach separation of the allele-specific hybridization products by flow cytometry (page 103, the first paragraph).

Regarding claim 24, Armstrong et al. teach probes specific for each of the SNPs coupled to different beads (Fig. 1; page 102, the last paragraph, continued on page 103).

Regarding claim 25, Armstrong et al. teach coupling of oligonucleotides specific for different polymorphisms to different bead sets (Fig. 1; page 102, the last paragraph, continued on page 103; page 103, third paragraph).

Regarding claim 27, Armstrong et al. teach obtaining genomic DNA samples from patients. The sample contained multiple alleles of the following genes: ADRB, APOE, CHRM2, COMT, HTR1B1, HTR1B2, KLK2 and UGT (page 104, first and second paragraphs).

Regarding claim 28, Armstrong et al. teach amplification of the genomic target nucleic acid (page 104, first and fourth paragraphs).

Regarding claim 29, Armstrong et al. teach denaturing of the double-stranded target nucleic acid into single strands (page 102, the last paragraph, continued on page 103; page 104, second paragraph).

Regarding claim 39, Armstrong et al. teach fluorescent beads (Abstract; page 102, last paragraph; page 103).

B) Armstrong et al. do not teach oligonucleotides with and without spacers.

C) Van Ness et al. teach compositions and methods for increasing specificity of hybridization reactions.

Regarding claim 22, Van Ness et al. teach an array of oligonucleotides immobilized on solid support, each of the nucleotides comprising a specificity spacer (col. 11, lines 53-67; col. 12, lines 1-37; Fig. 26). The specificity spacer may contain a base analog, so that a polymerase will continue through the spacer, or may contain an abasic residue, which terminates polymerase transcription (col. 40, lines 28-41). The specificity spacer may contain a component with 2-5 carbons (col. 40, lines 42-67; col. 41, lines 1-39). Oligonucleotides may have a plurality of specificity spacers (col. 41, lines 40-55). A specificity spacer site may be located approximately in a middle of a primer (col. 42, lines 53-67). Specificity spacers increase specificity of primer or probe annealing to targets (col. 42, lines 12-34). The solid support can take form of beads or membranes (col. 71, lines 65-67; col. 72, lines 1-14).

Van Ness et al. teach that combinations of oligonucleotides with different spacers may be used in any reaction involving hybridization, such as genetic screening, amplification reactions (col. 44, lines 59-67; col. 45, lines 1-3). In particular, such reactions include allele-specific PCR (amplification with allele-specific primers; col. 46, lines 27-33), DNA sequencing (col. 47, lines 38-

42), PCR (col. 49, lines 63-67), single-nucleotide primer extension (col. 51, lines 62-67; col. 52, lines 1-5; col. 55, lines 65-67; col. 56, lines 1-14; col. 61, lines 1-40). A single base polymorphism detection assay can be performed by hybridizing two different primers (differing in sequence and labels) to a target oligonucleotide, extending the primers using a polymerase, separating primers which were extended from primers which were not and determining the amounts of first and second labels in the primers that have been extended (col. 60, lines 34-67).

Regarding claims 24-26, 32, 37 and 38, Van Ness et al. teach oligonucleotides specific for two different base-pair mismatches, i.e., containing different spacers, coupled to different bead sets labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red. Oligonucleotides specific for the wild-type sequence did not have a spacer. After hybridization of the probes to target oligonucleotide the probes are denatured and fluorescence is measured in a fluorometer, and results are expressed as fluorescence ratios (col. 75, lines 49-62; col. 83, lines 10-67).

Regarding claim 27, Van Ness et al. teach polymorphism detection is samples containing CYP2D6 gene with 8 polymorphic sites (col. 97, lines 36-52).

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Regarding claim 31, Van Ness et al. teach HLA alleles (col. 63, lines 25-44).

Regarding claim 33 and 34, Van Ness et al. teach the spacer being nucleic acid bases (col. 40, lines 30-41; col. 44, lines 61, 62).

Regarding claim 35, Van Ness et al. teach the spacer in the middle of oligonucleotide sequence (col.. 42, lines 53-56).

Regarding claim 36, Van Ness et al. teach oligonucleotides with perfect sequence homology to their target oligonucleotides (col. 18, lines 39-41, lines 61-63; col. 19, lines 16-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used beads coupled to oligonucleotides with and without spacers of Van Ness et al. in the method of SNP typing of Armstrong et al. The motivation to do so, provided by Van Ness et al., would have been that using oligonucleotides with spacers provided increased specificity of primer or probe annealing to target (col. 42, lines 12-34), therefore allowing for accurate determination of allelic sequences.

20. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Armstrong et al. (Cytometry, vol. 40, pp. 102-108, June 1, 2000; cited in the previous office action) and Van Ness et al. (U. S. Patent No. 6,361,940 B1; cited in the previous office action) as applied to claim 22 above, and further in view of Long (Encyclopedia of Immunology, Roitt, I. M., Editor, Academic Press, San Diego, pp. 686-688, 1992; cited in the previous office action).

A) Claim 31 is drawn to the target oligonucleotide being an HLA allele.

B) Neither Armstrong et al. nor Van Ness et al. teach target nucleotides with HLA alleles.

C) Long teaches HLA class II alleles (DP, DQ and DR), determination of which is necessary for matching donor and recipient in organ transplantation, and typing of HLA alleles by PCR (Fig. 1; page 687, fourth and fifth paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used HLA allele-containing target oligonucleotide of Long in the combined method of Armstrong et al. and Van Ness et al. The motivation to do so, provided by Long, would have been that HLA allele determination was used for correct matching of organ transplants.

21. No claims are allowed.

Conclusion

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
February 10, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER